IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Springer et al. Art Unit : 1644
Serial No. : 09/945,265 Examiner : Maher M. Haddad, Ph.D.
Filed : August 31, 2001
Title : MODIFIED POLYPEPTIDES STABILIZED IN A DESIRED CONFORMATION AND METHODS FOR PRODUCING SAME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. COHEN

I, Edward H. Cohen, Ph.D., a citizen of the United States, residing in Belmont, Massachusetts, hereby declare as follows:

1. I am presently employed as a Principal Scientist by Dyax Corp. Dyax Corp. presently has a license to the above-reference application. My curriculum vitae is attached as Exhibit A and is summarized as follows: I received a Ph.D. in biology from Yale University in 1973. After a post-doctoral fellowship at the University of Washington, I was an assistant professor at Princeton University from 1974-1981. Subsequently, I was employed as a research scientist at a number of companies, including Integrated Genetics, Diagnostic Products Corporation, and Cytomed. Since 1995, I have been employed at Dyax Corp. in various capacities, including as a senior scientist, investigator, and principal scientist. Among other responsibilities, I am currently charged with the supervision and direction of the identification of therapeutics using phage display. I have co-authored numerous scientific papers and am a co-inventor on two issued U.S. patents as well as additional patent applications.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

6/2/04
Date of Deposit

Signature

Megan Crawley
Typed or Printed Name of Person Signing Certificate

2. I have read the above-referenced patent application and understand its contents. I have been advised and understand that claims 25-30, 73-80, and 82-88 of the above-referenced application are directed to antibodies or antigen binding fragments that specifically bind to integrin I-domains in an open conformation, that specifically bind to an LFA-1 integrin in the open conformation, or that bind to an integrin I domain in the open conformation but not to one in the closed conformation. Further, I have been advised and understand that the Examiner has rejected claims 25-30, 73-80, and 82-88 of the above-referenced application, in part, for lack of enablement.

3. Dyax Corp. personnel have used methods described in the application to make at least one antibody claimed in the application. Specifically, phage display technology is described at page 25 of the specification of the above-referenced application as one method for obtaining antibodies and antibody binding fragments that have the claimed properties. Members of a Fab phage display library were screened to identify phage that bind to a modified αL integrin I domain locked in the open conformation by the K287C/K294C mutations. Fab#57 is one exemplary Fab isolated by this screening method. We converted Fab#57 to a full length IgG ("IgG#57").

4. Figure 1 (Exhibit B) depicts results from surface plasmon resonance (SPR) assays. SPR detects biospecific interactions in real time between an agent in solution and a target immobilized on the surface of a chip. Changes in the mass at the surface of the BIACORE™ chip result in alterations of the refractive index of light near the surface and are indicative of a binding event. The changes in the refractivity generate a detectable signal, indicative of real-time interactions between the soluble agent and the target. Information from SPR can be used to provide an accurate and quantitative measure of the equilibrium dissociation constant (K_d), and kinetic parameters, including K_{on} and K_{off}, for the binding of the soluble agent to the immobilized target.

5. The top panel of Figure 1 depicts an SPR trace resulting from interactions between a soluble LFA-1 I domain locked in the open conformation by the K287C/K294C mutations and IgG#57 immobilized on a chip. The lower panel depicts a corresponding SPR trace resulting from interactions between a soluble LFA-1 I domain locked in the closed conformation by the L289C/K294C mutations and IgG#57 immobilized on a chip. Strong binding was observed between IgG#57 and the LFA-1 I domain locked in the open conformation (Kd = 10 nM or less). No detectable binding was seen between IgG#57 and the LFA-1 I domain locked in the closed conformation. The trace from the SPR instrument only shows a baseline level in the lower panel of Figure 1 where interactions with the LFA-1 I domain locked in the closed conformation were evaluated.

6. As Figure 1 confirms, this antibody (IgG#57) selectively binds to an I-domain in the open conformation, for example, as required by claims 25 and 30. The antibody also binds to an LFA-1 I domain in the open conformation, but not to an LFA-1 I domain in the closed conformation, for example, as required by claim 83. Thus, we have successfully used phage display to obtain an antibody with properties as claimed, for example, by claims 25, 30, and 83. These results demonstrate that one skilled in the art, reading the specification of the patent application, would have been able to identify antibodies or antigen binding fragments that have the claimed properties.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Date: June 1, 2004

Dr. Edward H. Cohen

Dr. Edward H. Cohen

20828292.doc